ULTRASONIC MECHANOTRANSDUCTION IN BONE REPAIR USING A COMPUTATIONAL MODEL

<u>Carine Guivier-Curien</u> (IRPHE, Marseille, France), Cécile Baron (ISM, Marseille, France),

Collaboration: Hieu N’Guyen, Salah Naili (MSME, Créteil, France)

ULTRASOUND (US) WAVES: DIAGNOSIS AND CARE

intensity

Thermal effects → Mechanical effects

High Intensity Focused Ultrasound
destroy

HIFU

Low Intensity Focused Ultrasound
repair

LIPUS

- LIPUS stimulates bone healing *(Duarte 1983, Heckman 1994, Hemery 2011,…)*
- FDA approval since 1994. Commercial device: Exogen

How do mechanical effects operate on bone healing?
Still an open question!
(Claes 2017, Padilla 2016)

Hypothesis: fluid shear stress on bone cells

Bone fracture

Bone remodeling

US stimulation at tissue scale → Mechano-transduction → biological response at cell scale

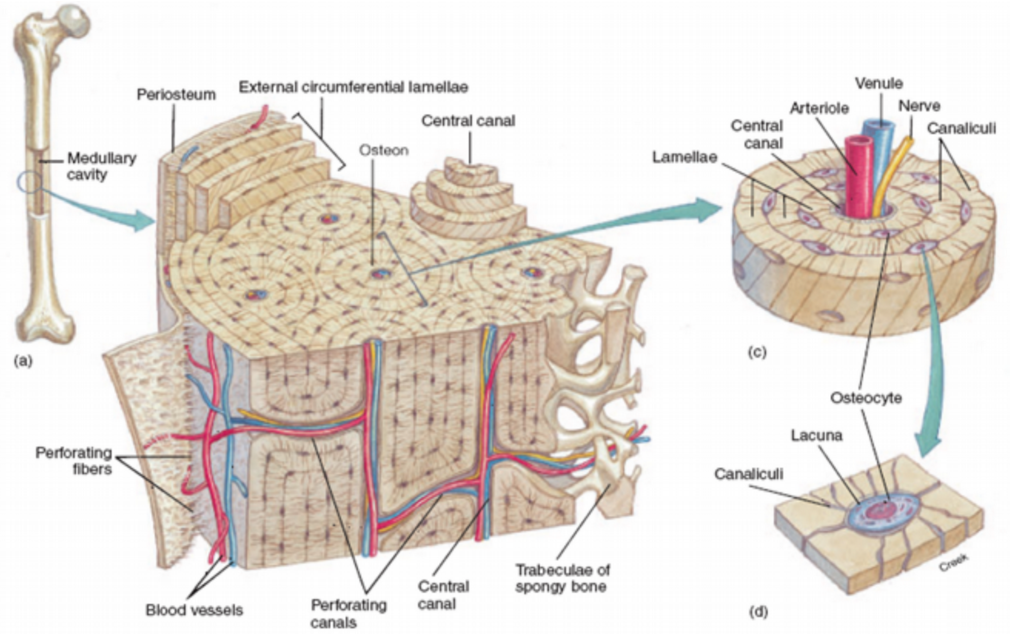
BONE, LIVING TISSUE

Cortical bone

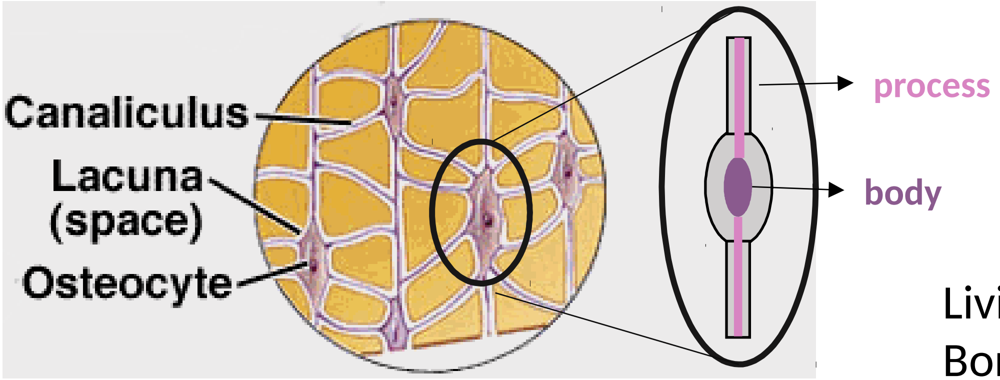
Tissue-scale
vascular porosity
(∅ 100µm)

Cellular scale
Lacuno-canalicular network (LCN) porosity
(∅ 10µm)

Double porosity level



Osteocytes: Cells immersed in an interstitial fluid



Pilots of bone healing
mechanosensors = **osteocytes**

Living tissue able to adapt to mechanical environment
Bone mechanotransduction under physiological loading *(Cowin 1991, Weinbaum 1994, Klein Nulend 1995)*

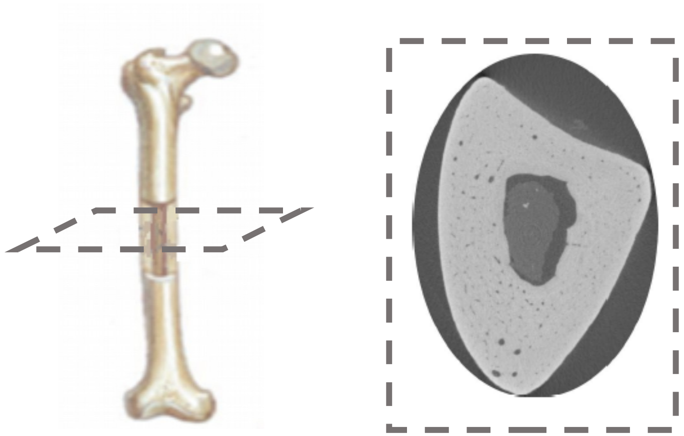
A MULTI-SCALE AND MULTI-PHYSICS MODEL

Hypothesis: US excitation at meso-scale level induces fluid shear stress on osteocytes at micro-scale level

A computational model is developed to investigate the question

A 2D biphasic medium model

- vascular porosity is geometrically reconstructed from µCT images (pixel size: 22.5µm)
- poroelastic medium (bone matrix and LCN) (Biot's model)
- Surrounding fluid = water



Wave equation in poroelastic medium *(Nguyen et al. 2010)*

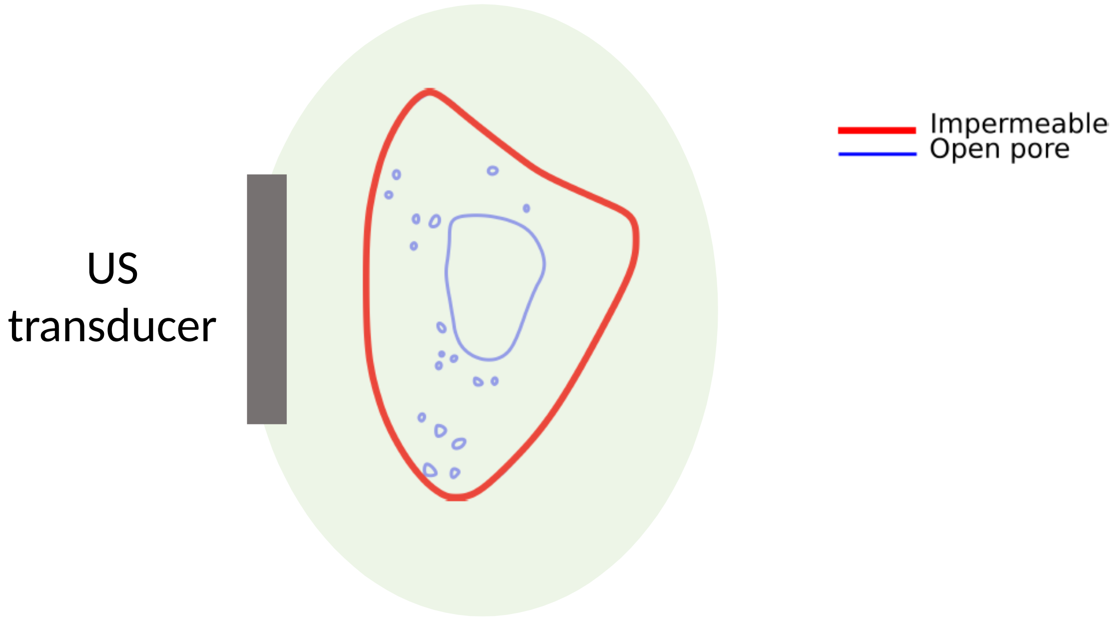
$$\nabla \cdot \boldsymbol{\sigma} = \rho\, \ddot{\boldsymbol{u}}_s + \rho_f \ddot{\boldsymbol{w}}\,,$$
$$-\nabla p = \rho_f\, \ddot{\boldsymbol{u}}_s + \mu\, \boldsymbol{k}^{-1}\, \dot{\boldsymbol{w}} + \boldsymbol{b}\, \ddot{\boldsymbol{w}}$$

p : fluid pressure in pores
u_s : displacement of solide
ρ : mixture density
σ : total stress tensor
µ : fluid viscosity

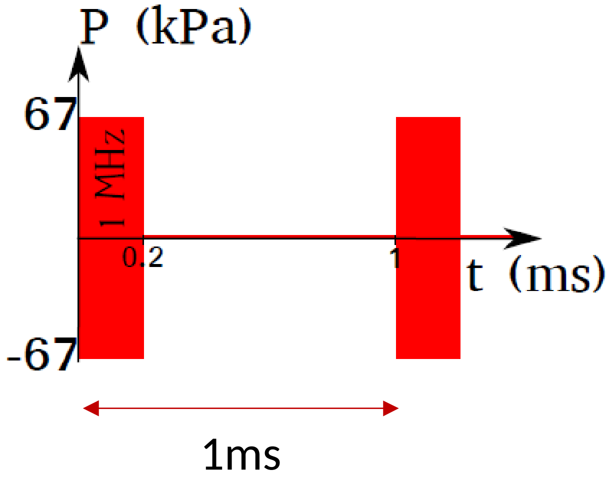
ρ_f : fluid mass density
w : relative displacement between fluid and solid
k: anisotropic permeability tensor
b= (ρ_f /∅) a , with ∅ porosity and a tortuosity tensor

A MULTI-SCALE AND MULTI-PHYSICS MODEL

Boundary conditions
Continuity of pressure and stress fields
Open pore conditions

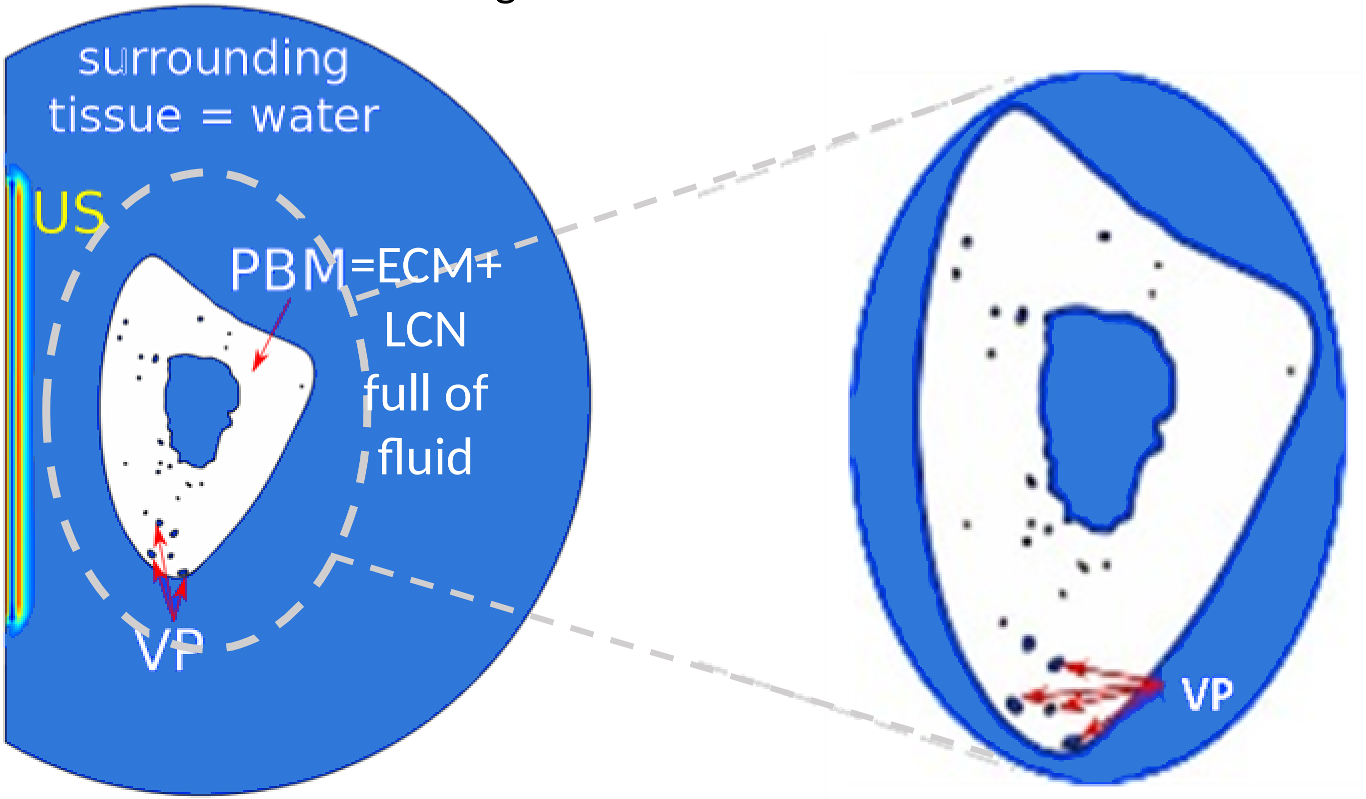


Acoustic Stimulation: adapted from Exogen
Transducer: 20mm
Pressure: 67 kPa
US frequency: 1MHz
Pulse frequency: 1kHz
20% duty cycle



A MULTI-SCALE AND MULTI-PHYSICS MODEL

2D geometrical model

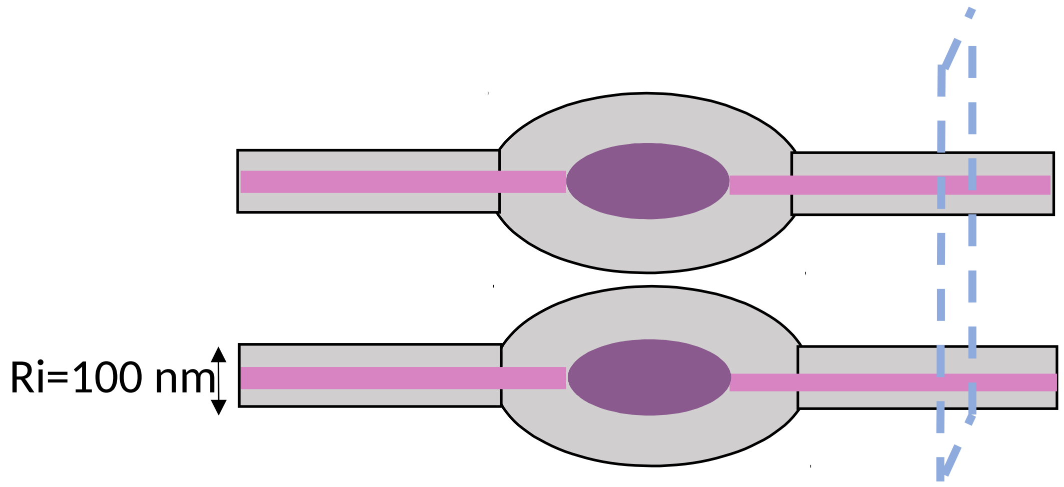


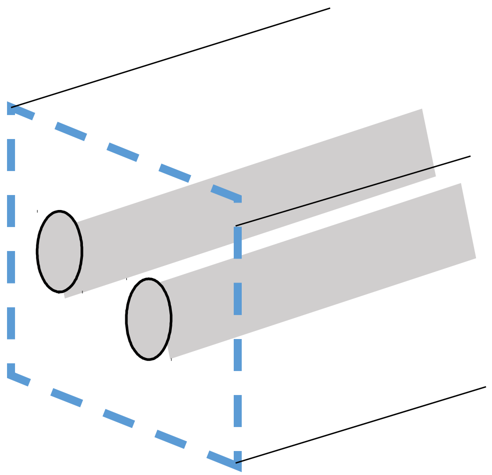
PBM= poroelastic bone matrix
ECM= extra cellular matrix
VP= vascular porosity
US=Ultrasound Stimulation
LCN= lacuno-canalicular network

Question:
How to calculate shear stress on osteoctyes and which value of permeability for LCN?

Wide range of values in literature:
10^{-25} - 10^{-17} m^2
(Cardoso et al. 2013)

MECHANICAL SHEAR STRESS ON OSTEOCYTES





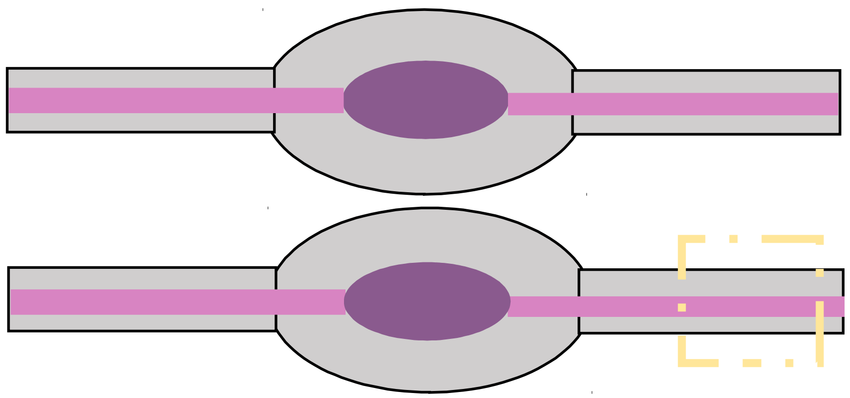
In Kozeny-Carman Theory:

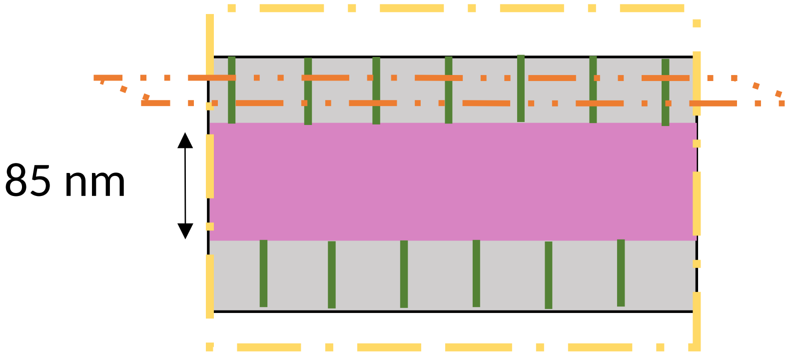
Poiseuille flow in a network of aligned cylindrical tubes

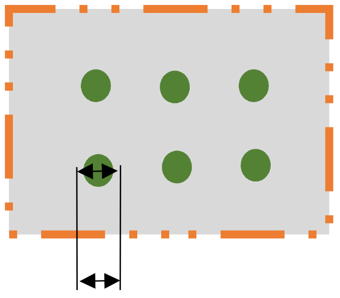
$$k_{\mathrm{KC}} = \phi R_i^2/8 = 1.56 \times 10^{-17}\mathrm{m}^2$$

$$\tau_{\mathrm{KC}} = \frac{R_i \mu |\boldsymbol{v}_{\mathrm{Darcy}}|}{2k_{\mathrm{KC}}}$$

MECHANICAL SHEAR STRESS ON OSTEOCYTES







Wang and Tarbell (1995): fluid flow in an annulus through a network of transverse fibers (GAG fibers)

Permeability from Smit et al. (2002): from experimental and numerical results

$$\tau_{\mathrm{WT}} = \frac{\mu |v_{\mathrm{Darcy}}|}{\sqrt{k_{\mathrm{S}}}}$$

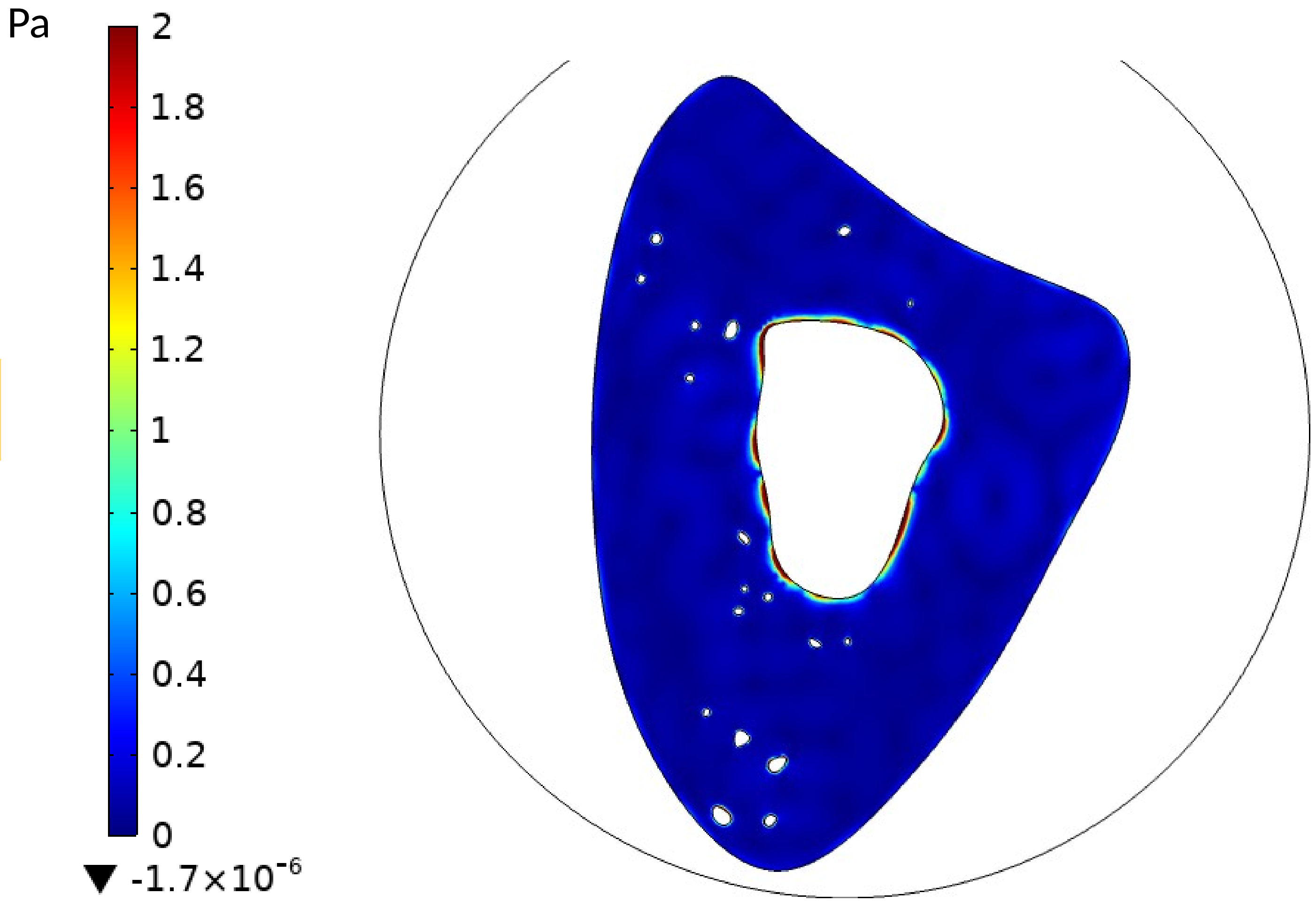
$$k_{\mathrm{S}} = 2.2 \times 10^{-22} \mathrm{m}^2$$

RESULTS

- Wall shear stress patterns during 10 pulse cycles (=10ms)

- Homogeneous pattern in poroelastic medium
- Local peak of stress near vascular pores and endosteum

τ_{WT}



RESULTS

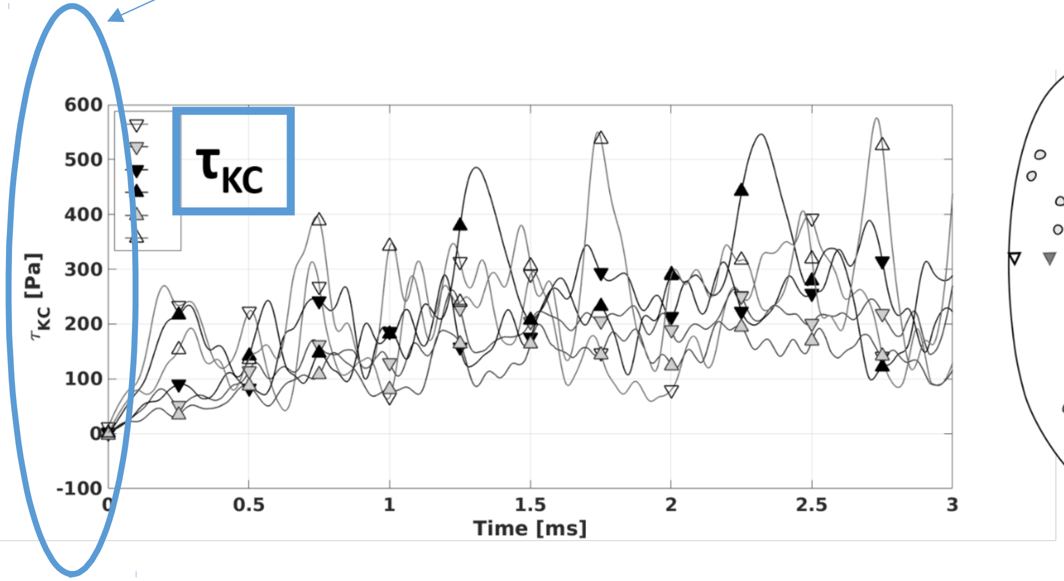
- Moving average on 1µs (=1period of US signal) for 6 points in the domain (before and after endosteum in the US trajectory) for both wall shear stress calculations

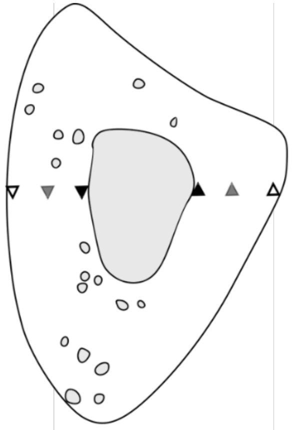
- $\tau_{kc} \approx 10^2$ Pa
- $\tau_{wt} \approx 10^{-1}$ Pa

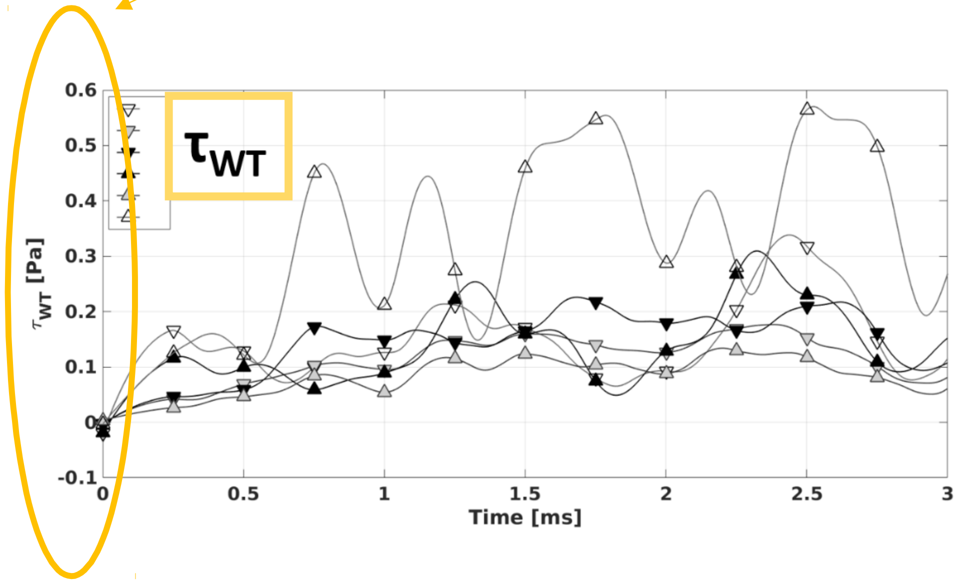
→ Kozeny-Carman model seems not to be adapted ? Since activation of osteocytes is found at a level of 0.8 to 3 Pa for a physiological loading *(Weinbaum et al. 1994)*

≈ 10^2 Pa

≈ 10^{-1} Pa





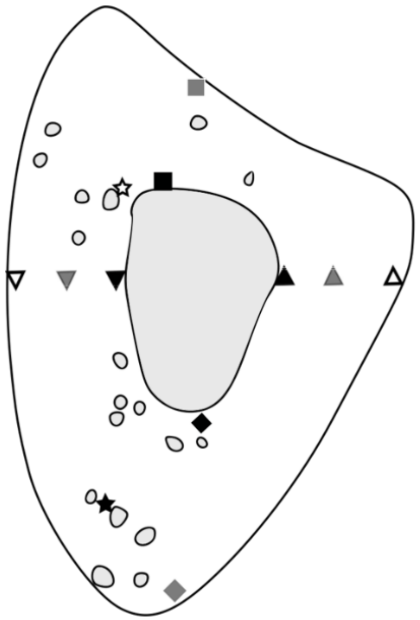


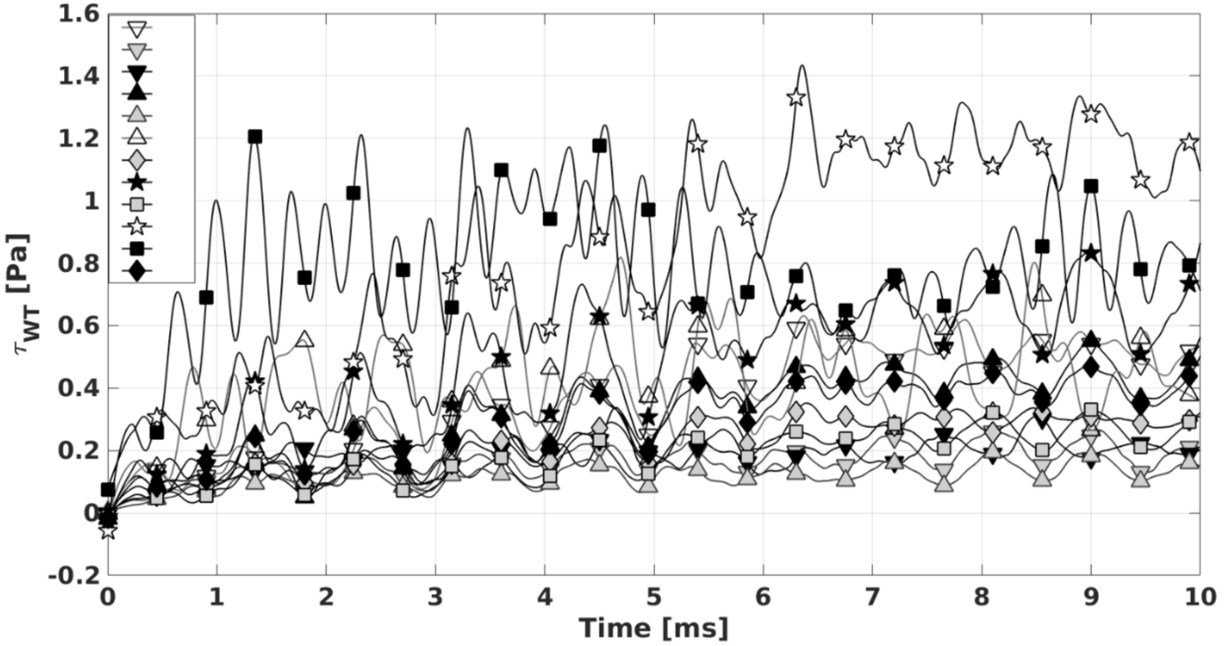
RESULTS/DISCUSSION

τ_{WT}

Results on 10 cycles
for 12 selected points
in the domain

Values of τ_{WT}





- No cumulative effect over 10 cycles

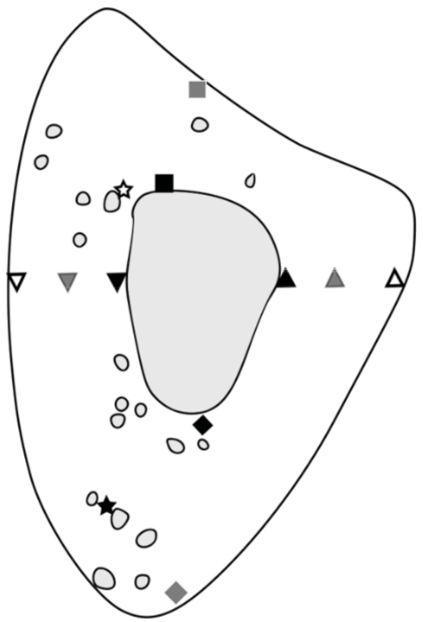
- Model: 10ms versus Exogen: 20min of treatment a day during several weeks

… far from clinical stimulation? Biological experimental study is developed

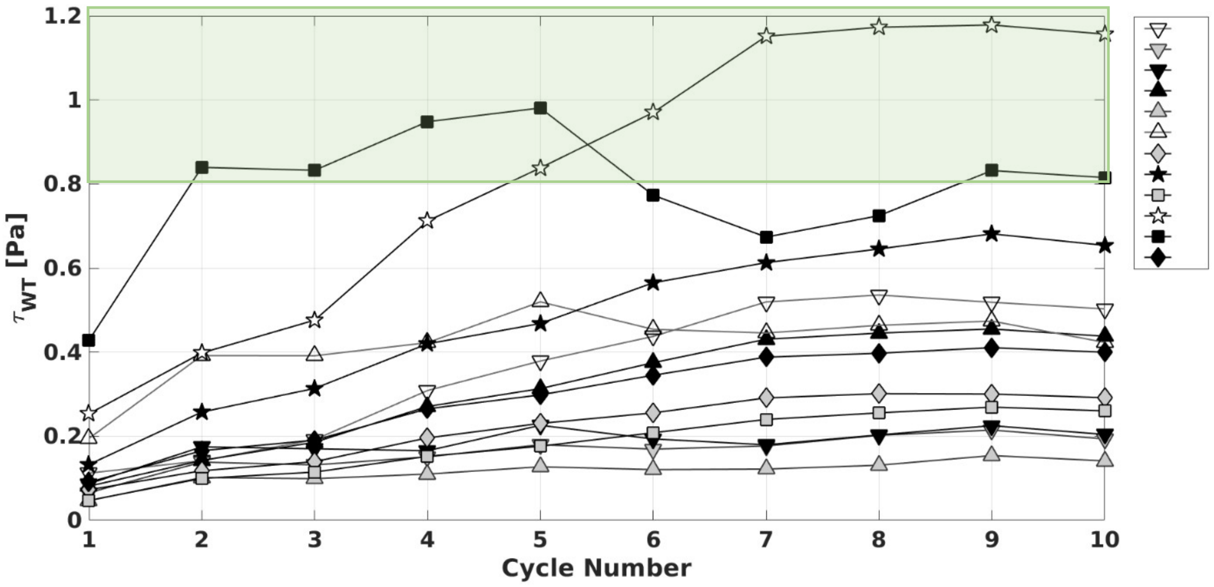
RESULTS/DISCUSSION

τ_{WT}

Results on 10 cycles for 12 selected points in the domain



Averaged values per cycle



shear stress range for osteocyte activation under physiological load (f=1-10Hz) *(Weinbaum et al. 1994)*

- Values smaller than range reported in literature (0.8 to 3 Pa)

- Lower limit of the range of physiological values

BUT: Pulse frequency and US loading frequency are 10^{3-6} higher than this of *Weinbaum et al. 1994*

Bacabac et al. 2004 : high frequency and low-amplitude is equivalent to low frequency and high amplitude

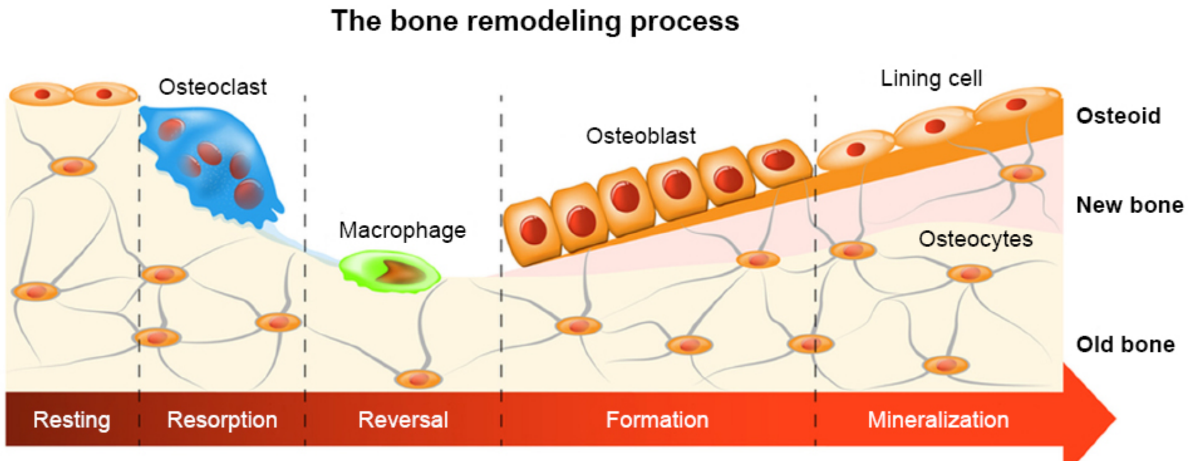
→ importance of rate of shear stress

CONCLUSIONS & PERSPECTIVES

A model to better understand US mechanical effect in bone healing by LIPUS
Values of shear stress to activate osteocytes ↔ LCN ≠ aligned tubes (too simplistic?)
Potential role of GAG fibers in mechanotransduction *(Han et al. 2004, Barra et al. 2010)*

Perspectives:

- Acoustic parameters to explore in order to better understand the influence of each one and thus to better care
- Local high shear stress on pores and endosteum: role/action of lining cells in LIPUS?

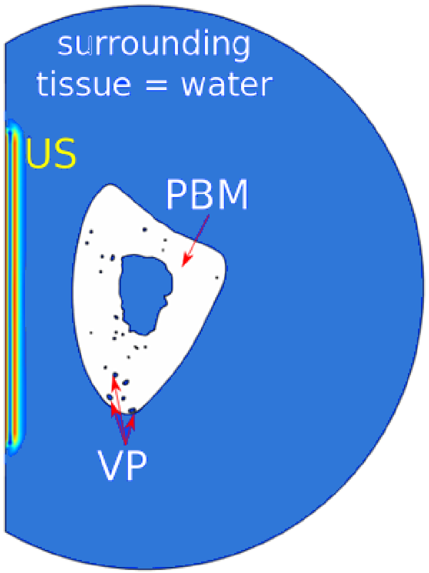


ULTRASONIC MECHANOTRANSDUCTION IN BONE REPAIR USING A COMPUTATIONAL MODEL

Thank for your attention

Any questions?

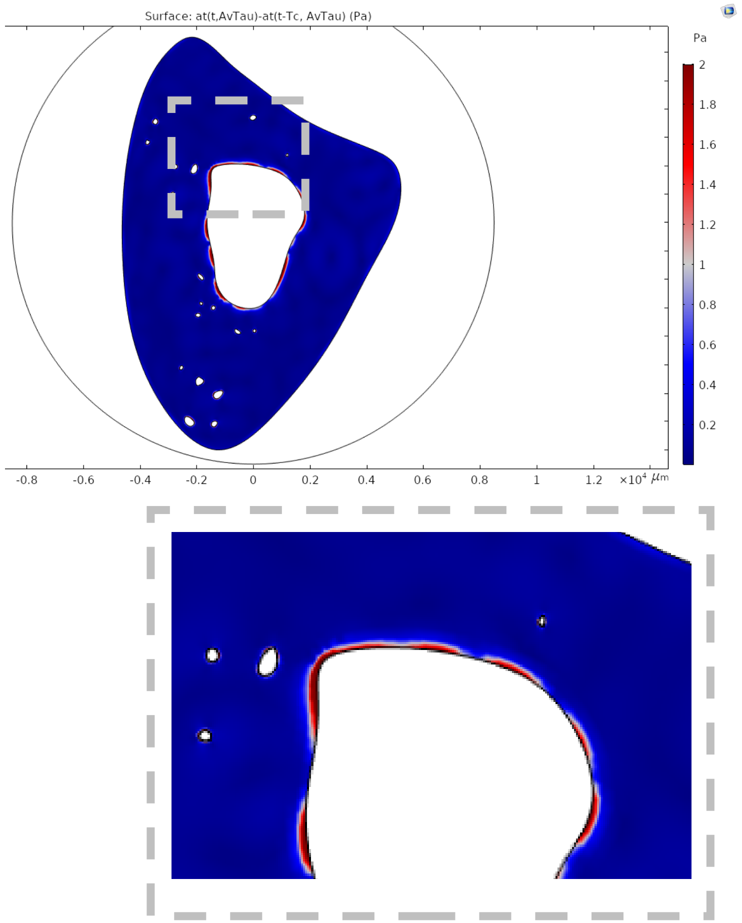
carine.guivier@univ-amu.fr,
cecile.baron@univ-amu.fr



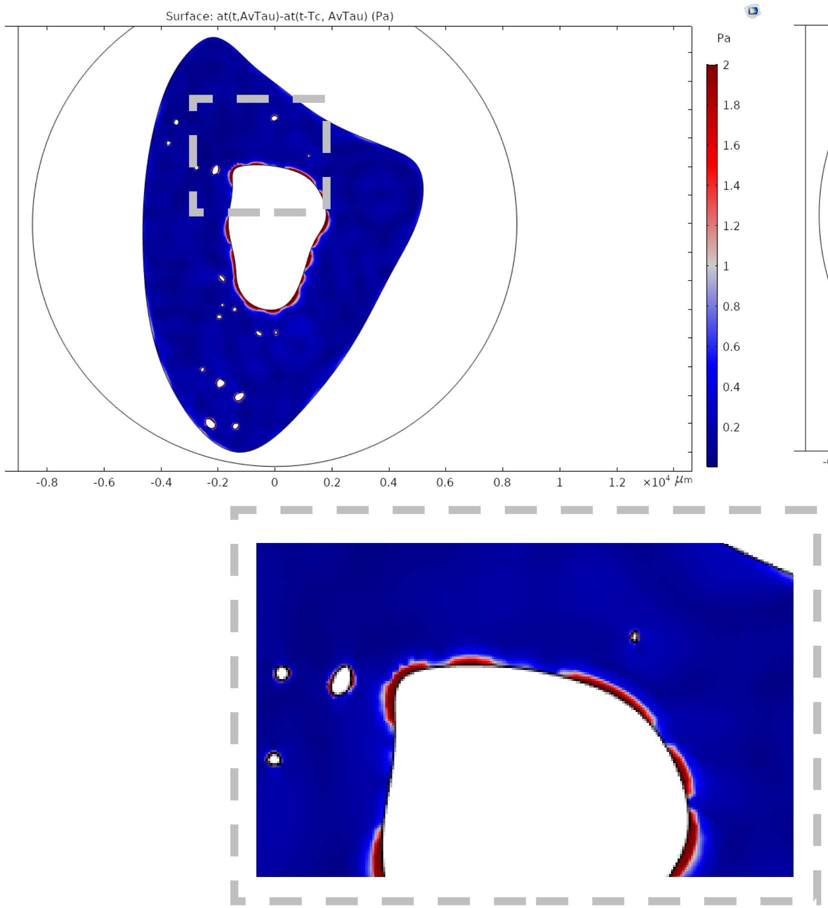
ESB 2019
July 7-10, 2019
Vienna, Austria

RESULTS

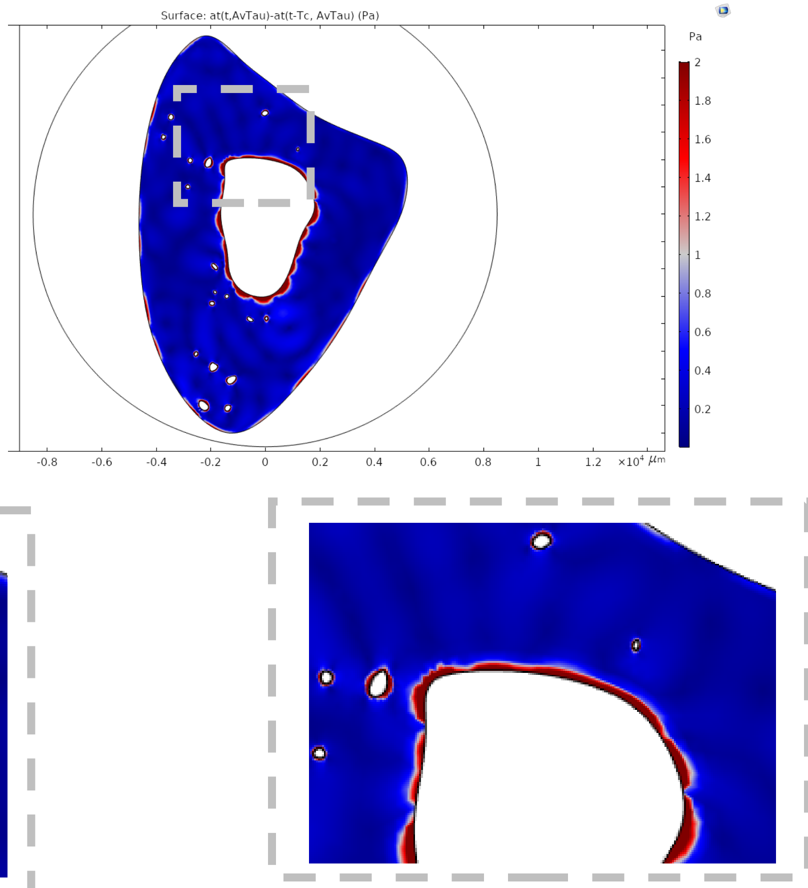
- 3 cycles of 1ms simulated for both cases. Wall shear stress levels in LCN
- Local peak of stress near pores and endosteum



End of cycle 1



End of cycle 5



End of cycle 10